REMARKS

Amendments to the Claims

Claim 2 and Claim 6 have been canceled. Claims 1, 3-5, 7, 8 and 11 have been amended. New Claims 12-20 have been added.

Claims 1, 3-5, 7-8 and 11 have been amended to clarify that the ankylosis treated is "TNFα-mediated joint ankylosis." Support for these amendments is found in the specification, for example, at page 16, lines 15-18; page 19, lines 7-9; and page 57, line 16 to page 59, line 14.

Claims 1, 5, 7-8 and 11 have been further amended to recite that the antibody administered is a "TNFα-inhibiting amount of an anti-TNFα chimeric antibody." Claim 3 has been further amended to recite that the antibody administered is a "TNFα-inhibiting amount of an anti-TNFα chimeric monoclonal antibody." Support for these amendments is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 17-24.

Claims 1 and 5 have been further amended to recite that the administered antibody competitively inhibits binding of human TNFα to anti-TNFα chimeric monoclonal antibody cA2. Support for the amendments to Claims 1 and 5 is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 17-24.

Claim 3 has been further amended to recite "... administering to the human an effective TNFα-inhibiting amount of anti-TNFα chimeric monoclonal antibody cA2." Support for this amendment to Claim 3 is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 7-24.

Claim 4 has been further amended to recite "...administering to the human at least one anti-TNFα chimeric monoclonal antibody cA2, or an antigen-binding fragment thereof." Support for this amendment to Claim 4 is found in the specification, for example, at page 19, lines 7-24.

New Claim 12 is directed to the method of Claim 1 wherein said anti-TNF-α antibody binds with high affinity to a neutralizing epitope of human TNF-α. Support for new Claim 12 is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 17-24.

New Claim 13 is directed to the method of Claim 1 wherein said anti-TNFα antibody binds to a neutralizing epitope of human TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis. Support for new Claim 13 is found in the specification, for example, at page 10, lines 8-15, and

Example X, particularly page 80, line 24 to page 81, line 12.

New Claim 14 is directed to the method of Claim 1 wherein said anti-TNFα antibody is administered to the human by means of parenteral administration. Support for new Claim 14 is found in the specification, for example, at page 59, lines 23-29.

New Claim 15 is directed to the method of Claim 1 wherein said anti-TNFα antibody is administered to the human by means of intravenous administration. Support for new Claim 15 is found in the specification, for example, at page 59, lines 23-29.

New Claim 16 is directed to the method of Claim 1 wherein said anti-TNFα antibody is administered to the human by means of subcutaneous administration or intramuscular administration. Support for new Claim 16 is found in the specification, for example, at page 59, lines 23-29.

New Claim 17 is directed to the method of Claim 1 wherein said anti-TNFα antibody is administered to the human orally. Support for new Claim 17 is found in the specification, for example, at page 59, lines 23-29.

New Claim 18 is directed to the method of Claim 1 wherein said TNFα-inhibiting amount of the anti-TNFα antibody comprises a single or divided dose of about 0.1 - 50 mg/kg. Support for new Claim 18 is found in the specification, for example, at page 60, lines 7-24.

New Claim 19 is directed to the method of Claim 18 wherein said single or divided dose is selected from the group consisting of: about a 0.1 - 1 mg/kg dose, about a 1.0 - 5 mg/kg dose, about a 5 - 10 mg/kg dose and about a 10 - 20 mg/kg dose. Support for new Claim 19 is found in the specification, for example, at page 60, lines 7-24.

New Claim 20 is directed to the method of Claim 1 further comprising administering to the human an effective amount of a therapeutic agent selected from the group consisting of: radiotherapeutics, cytotoxic drugs, monoclonal antibodies, chimeric antibodies, antibody fragments, antibody regions, lymphokines, cytokines, hemopoietic growth factors and immunoglobulins. Support for new Claim 20 is found in the specification, for example, at page 62, lines 4-23 and page 63, lines 3-7.

No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Correspondence Address

Please note that the undersigned Attorney has taken over responsibility for this application. A Notice of Change of Contact Attorney is being filed herewith.

Amendments to the Specification

The Examiner states that the application is to be reviewed and all spelling, trademarks, and like errors corrected, and that the first line of the specification should be amended to update the status of the priority documents.

Applicants have amended the specification to comply with the requirement to indicate trademarks and to update the status of a related application. In addition, Applicants have amended the paragraph at page 58, line 1 through page 59, line 14 to recite ankylosis. Support for this amendment is found in the title; originally-filed Claims 1-8 and 11; and page 131, line 13. Applicants have also corrected typographical errors in the specification. Support for the typographical errors is found throughout the specification. No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Sequence Listing

Applicants thank the Examiner for noting that the instant application is in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Priority

The Examiner states that "[t]he filing date of the instant claims is deemed to be the filing date of the instant application 10/044,534, filed 1/10/02." The Examiner further states that:

> The only disclosure of the term 'ankylosis' in the specification as-filed appears on page 131, line 13 which discloses: "Patients with severe physical incapacity (Stenibrocker class IV) or with clinically evident joint ankylosis were excluded." Therefore, it appears that the disclosure of the specification as-filed does not support the current claimed methods, as recited.

Applicants respectfully disagree. The instant claims are entitled to claim the benefit of priority application USSN 07/670,827 (filed March 18, 1991). Priority application USSN 07/670,827 provides sufficient written description and enablement for treating TNFα-mediated human disease, including joint ankylosis. USSN 07/670,827 discloses that the "[h]igh affinity chimeric anti-TNFα mAbs of the present invention, which have potent TNFα neutralizing activity, including TNFα-neutralizing fragments thereof, are useful as therapeutic agents for TNFα-mediated human disease...." (page 10, line 22-25) In addition, the specification of this priority application teaches and enables treatment of a representative number of species of the genus "TNFα-mediated diseases" including "rheumatoid arthritis" with the claimed antibodies. (See USSN 07/670,827 at page 39, line 20 to page 40, line 9 and page 10, lines 22 to page 11, line 4)

Ankylosis is a TNFα-mediated disease. Ankylosis is defined as "stiffening or fixation of a joint as the result of a disease process, with fibrous or bony union across the joint." (Stedman's Medical Dictionary 93 (26th ed. 1995) (Exhibit A)). As indicated in The Merck Manual of Diagnosis and Therapy, which was cited by the Examiner, ankylosis may occur as the result of rheumatoid arthritis, which is an TNFα-mediated inflammatory disease of the joints. Although there is not a specific example in the 07/670,827 specification directed to treatment of TNFα-mediated joint ankylosis, the mechanism of treatment would be the same regardless of the TNFα-mediated disease.

Therefore, the priority application 07/670,827 (filed March 18, 1991) provides sufficient written description and enablement for treating ankylosis, and Applicants are entitled to claim the benefit of it. This priority application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120.

Further, at the very least, Applicants are entitled to priority to October 18, 1994. Applicants note that the Examiner has cited Applicants' own priority patent (Le *et al.* U.S. Patent No. 5,698,195) as prior art. The Examiner states in the 35 U.S.C. § 102 (b) rejection that "[t]he claimed functional limitations would be inherent properties of the referenced methods [taught in U.S. Patent No. 5,698, 195] to treat rheumatoid arthritis with recombinant cA2-specific antibodies." (Office Action at page 6) Le *et al.* (5,698,195) was filed October 18, 1994 and published December 16, 1997 and it also claims the benefit of priority to the same U.S. priority

application (U.S. Serial No. 07/670,827) as the subject application. As discussed below, in order to qualify as an anticipatory reference, a reference must meet the requirement of enablement.

Therefore, if Applicants' disclosure in U.S. Patent No. 5,698,195 is sufficient to qualify as prior art, then U.S. Patent No. 5,698,195 is sufficient to support the claims in the subject application, and the claims, at the very least, are entitled to the benefit of priority to its filing date of October 18, 1994. This priority patent has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120.

Moreover, U.S. Patent No. 5,698,195 provides additional support for the claimed methods of treating TNFα-mediated diseases. For instance, Examples XX and XXIV disclose the clinical effectiveness of treating a known TNFα-mediated disease, rheumatoid arthritis, by administering the recited anti-TNFα antibodies. Examples XXI and XXV disclose the clinical effectiveness of treating a known TNFα-mediated disease, Crohn's disease, by administering the recited anti-TNFα antibodies. Example XXIII discloses the clinical effectiveness of treating a known TNFα-mediated disease, ulcerative colitis, by administering the recited anti-TNFα antibodies. This disclosure provides even further support for the claimed treatment methods.

Objection to the Specification Under 37 C.F.R. § 1.75(d) and M.P.E.P. § 608.01(l)

The Examiner states that "[t]he specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R 1.75 § (d)(1) and M.P.E.P. § 608.01(l). The Examiner further state that:

> It appears that the only description of "methods of treating ankylosis" appears in the Title and original Claims. The only disclosure of the term "ankylosis" in the specification as-filed appears on page 131, line 13 which discloses: "Patients with severe physical incapacity (Steinbrocker class IV) or with clinically evident joint ankylosis were excluded." Applicant is required to amend the specification to provide proper antecedent basis for the claimed recitation of "ankylosis". Alternatively, applicant is invited to identify the written support for the claimed recitation of "ankylosis" in the specification as-filed.

Applicants have amended the paragraph at page 58, line 1 through page 59, line 14 to provide further literal support for ankylosis, thereby obviating the objection. (37 C.F.R. §

1.75(d) and M.P.E.P. § 608.01(l)) Moreover, the claims have been amended to recite "joint ankylosis." Reconsideration and withdrawal of the objection are respectfully requested.

Rejection to Claims 1, 3-5, and 11 Under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5 and 11 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that:

> It is apparent that the cA2 antibody is required to practice the claimed invention. Asa required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line/hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

Applicants respectfully disagree. The cA2 antibodies can be obtained from publicly available material with only routine experimentation and a reliable screening test. Therefore, the biological materials for cA2 antibodies need not be, and have not been, publicly deposited.

Applicants direct the Examiner's attention to the Federal Circuit decision in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (a copy of which is attached as Exhibit B for the Examiner's convenience). The claims at issue in *In re Wands* recited methods for an immunoassay using high affinity monoclonal antibodies that the Appellants found to have unexpectedly high sensitivity and specificity. The position of the PTO was that the data showed that the production of the antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make them. However, the court in *In re Wands* disagreed, noting that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening," as long as the experimentation was not undue. *Id.* at 1404. The court concluded that undue experimentation would not be required to practice the claimed invention.

The court first stated that "Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples." *Id.* at 1406. The

court further stated that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* The court in *In re Wands* recognized that the nature of monoclonal antibody technology is such that it involves screening hybridomas to determine which ones secrete antibodies with desired characteristics, and that practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. *Id.* The court went on to state that "in the monoclonal antibody art it appears that an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen." *Id.* at 1407.

Chimeric A2 (cA2) is a monoclonal anti-TNFα antibody consists of the antigen binding variable regions of the high-affinity neutralizing mouse antihuman TNF IgGl antibody, designated A2, and the constant regions of a human IgGl, kappa immunoglobulin. The human IgGl Fc region improves allogeneic antibody effector function, increases the circulating serum half-life, and decreases the immunogenicity of the antibody. The avidity and epitope specificity of the chimeric A2 is derived from the variable regions of the murine A2. Chimeric A2 neutralizes the cytotoxic effect of both natural and recombinant human TNF. (See, for example, instant Detailed Description at page 34, line 10 to page 35, line 4). Examples I-IX teach the production, characterization and expression of the cA2 antibody. Examples X-XII teach assays for screening the cA2 antibody.

In considering the factors enumerated in *In re Wands*, Applicants' disclosure provides considerable direction and guidance on how to practice their invention, and presents numerous working examples. For example, the sequences of the variable regions of the antibodies are disclosed in Figures 16A-16B. In addition, the specification teaches methods of producing the claimed cA2 antibodies according to the present invention (See instant Detailed Description at page 32, lines 7 through 24; page 34, line 10 through page 35, line 4; and Examples III-IX).

Additionally, Applicants' disclosure teaches methods of cloning a polynucleotide encoding an anti-TNF variable or constant region. (See, for example, instant Detailed Description at page 28, line 3 through page 31, line 2). Furthermore, it teaches that preferred anti-TNF monoclonal antibodies include those which will competitively inhibit *in vivo* the binding to human TNFα of anti-TNFα murine monoclonal antibody A2, chimeric monoclonal antibody

cA2, or an antibody having substantially the same specific binding characteristics, as well as fragments and regions thereof. (See, for example, page 19, lines 17-20). It also teaches preferred methods for determining monoclonal antibody specificity and affinity (See, for example, instant Specification at page 19, line 25 through page 20, line 2, and Examples X and XI). In addition, there was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

Thus, a person of skill in the art would not be subject to undue experimentation without a reasonable expectation of success in order to make and screen cA2 antibodies which would have these claimed elements.

A deposit is not required because the disclosure is sufficient to enable production of the claimed antibodies. No more is required. The Examiner has failed to present any evidence which suggests that anti-TNFα antibodies with the claimed specificity are unusually difficult to isolate.

In addition, Applicants' written specification fully enables the practice of the claimed invention because the claimed cA2 antibodies can be made from readily available starting materials using methods that are well known in the art and taught in detail in the specification. As discussed above, and as detailed in the specification, cA2 is derived from the A2 antibody. The A2 antibody was publicly available at least as of April 19, 1992. (See Declaration of Jan Vilcek M.D., hereinafter "Vilcek Declaration" at ¶ 5)

Furthermore, as noted by the Examiner, the claims encompassing the cA2 antibody issued in the related priority patent U.S. Patent No. 5,919,452 and were determined to be enabled. As is clear from the prosecution history, no deposit was necessary to satisfy the enablement requirement. Moreover, Applicants' argument that claims reciting cA2 are enabled and a cA2 deposit is not required has also been found persuasive in other related U.S. Applications, including USSN 09/756,301, now U.S. Patent No. 6,790,444.

As discussed above, the instant Specification and figures, together with what was known and available in the art, provide ample teachings such that one of skill in the art would not be subject to undue experimentation in order to make or use the claimed antibodies. Thus, the skilled artisan is enabled to make and use the claimed invention commensurate in scope with the claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1-11 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 1-11 under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for the 'TNFα-specificity'; does not reasonably provide enablement for any 'TNF-specificity' having such specificities."

Applicants respectfully disagree. As noted above, Applicants have canceled Claims 2 and 6. Further, to expedite prosecution, Applicants have amended Claims 1, 3-5, 7-8 and 11 to recite that the claimed antibodies are anti-TNFα antibodies. In the specification, Applicants have exemplified that the cA2 antibody competitively inhibits and binds with high affinity a neutralizing epitope of human TNFα. Therefore, particularly as amended, the claims are enabled.

However, it should also be noted that anti-TNFα antibodies are not the only antibodies supported by the specification. As indicated in the specification, the present invention provides anti-TNF compounds and compositions comprising anti-TNF antibodies (Abs) and/or anti-TNF peptides which inhibit and/or neutralize TNF biological activity *in vitro, in situ* and/or *in vivo*, as specific for association with neutralizing epitopes of human tumor necrosis factor-alpha (hTNFα) and/or human tumor necrosis factor β (hTNFβ). (Page 16, lines 15-19) Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1, 3-5 and 11 Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1, 3-5 and 11 as indefinite in the use of "cA2" as the sole means of identifying the claimed antibody. Specifically, the Examiner states that "[t]he use of 'cA2' monoclonal antibody as the sole means of identifying the claimed antibody renders the claim indefinite because 'cA2' is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation [ ] to define completely distinct hybridomas / cell lines."

Applicants respectfully traverse this rejection. cA2 is not used as the sole means of identifying the antibody in the claims. The claims and specification provide a great deal of description regarding cA2's structure and properties. As amended, the claims explicitly state that the antibody is a chimeric anti-TNFα monoclonal antibody. Further, the specification clearly discloses that the antibody is a chimeric anti-TNFα monoclonal antibody, and provides a detailed

disclosure of the production, structure and function of cA2. (Specification at page 17, lines 2-8; page 19, lines 7-16; page 26, lines 21-28 and page 34, line 12 to page 35, line 4) For instance, Examples I-IX teach the production, characterization and expression of the cA2 antibody and Examples X-XII teach assays for screening the cA2 antibody.

Moreover, "cA2" is recognized by those skilled in the art as a unique identifier of Applicants' chimeric anti-TNFα monoclonal antibody. A number of scientific articles and press releases refer to Applicants' claimed monoclonal antibody as "cA2." (See, for example, Elliott, M. J. *et al.*, "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis Rheum, 36*:1681-1690 (1993) (Exhibit C); Walker, R.E., "Inhibition of Immunoreactive Tumor Necrosis Factor-alpha by a Chimeric Antibody in Patients Infected with Human Immunodeficiency Virus Type 1," J. *Infect. Dis., 174*(1):63-8 (1996), abstract from AIDSLINEMED/96261994 (Exhibit D); and "New Monoclonal Antibody Effective Treatment For Crohn's Disease Therapy," Doctor's Guide (May 13, 1997), http://www.docguide.com/dg.nsf/PrintPrint/815D53A771190A4285256496004B0796 (Exhibit E)). These references are representative of the general knowledge of one skilled in the art and demonstrate that the identifier "cA2" clearly defines the claimed product. Thus, the cA2 antibody is well known in the art.

Indeed, a number of claims have issued which refer to the instant chimeric anti-TNFα monoclonal antibody as cA2. For example, the claims of related U.S. Patent No. 6,284,471, which has the same priority date and has a substantially identical specification as the instant application, recite cA2. (A copy of the claim set of U.S. Patent No. 6,284,471 is attached hereto as "Exhibit F" for the Examiner's convenience).

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1-11 Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1-11 as being "indefinite in the recitation of 'methods of treating ankylosis' because the metes and bounds of the targeted patient populations and conditions/disorders are ill-defined and ambiguous." Further, the Examiner states that:

> As pointed out above, it appears that the only description of "methods of treating

> ankylosis" appears in the Title and original Claims. The only disclosure of the term "ankylosis" in the specification as-filed appears on page 131, line 13 which discloses: "Patients with severe physical incapacity (Stenibrocker class IV) or with clinically evident joint ankylosis were excluded." Therefore, it appears that the disclosure of the specification as-filed does not support the current claimed methods, as recited. Applicant is invited to clarify the metes and bounds of the claimed "methods of treating ankylosis."

As discussed above, Claims 1, 3-5, 7-8 and 11 have been amended to recite "TNFα-mediated joint ankylosis," thereby obviating the rejection. Claims 2 and 6 have been canceled. Claims 9 and 10 are dependent on Claim 1 and, therefore, contain the same element. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1-11 Under 35 U.S.C. § 102(b)

The Examiner has rejected Claims 1-11 as being anticipated by Le *et al.* (U.S. Patent No. 5,698,195). The Examiner states that:

> Le et al. teach methods of treating TNF-related pathologies, including rheumatoid arthritis (see column 34, line 53 and Claims) with TNF-α-specific antibodies, including recombinant and chimeric antibodies and the cA2 antibody specificity of the instant invention (see entire document, including Summary of the Invention, Detailed Description of the Invention and Claims). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to treat rheumatoid arthritis with recombinant cA2-specific antibodies. A species anticipates a claim to a genus. See MPEP 2131.02.

Applicants' own priority patent Le *et al.* (5,698,195) is not prior art under 35 U.S.C. § 102 (b) because it was not published more than one year before Applicants' priority date. First, as indicated above, Applicants are entitled to priority to U.S. Application Serial No. 07/670,827 (filed March 18, 1991). Le *et al.* (5,698,195) was filed October 18, 1994, and published December 16, 1997, and it also claims the benefit of priority to the same U.S. priority application (U.S. Serial No. 07/670,827) as the subject application. Second, Applicants are entitled to claim the benefit of priority of this cited reference.

Moreover, "[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *Elan Pharm. Inc. v. Mayo Foundation for Medical and Education Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (citation omitted). As stated in the MPEP at § 2121.01:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'...."

(Quoting *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

> The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation.

(Citing *Elan Pharm. Inc. v. Mayo Foundation for Medical and Education Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

Therefore, if Applicants' disclosure in their priority patent U.S. Patent No. 5,698,195 is sufficient to qualify as prior art, then U.S. Patent No. 5,698,195 is sufficient to enable the claims. As noted by the Examiner, the claimed functional limitations are inherent in the teachings of the priority patent. Thus, the claims at the very least, are entitled to the benefit of priority to the filing date of the 5,698,195 patent, October 18, 1994. Hence, Applicants' priority patent, U.S. Patent No. 5,698,195, is not prior art. Reconsideration and withdrawal of the objection are respectfully requested.

Rejection to Claims 1-11 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-11 as being unpatentable over Le *et al.* (U.S. Patent No. 5,698,195) in view of The Merck Manual of Diagnosis and Therapy, Seventeenth Edition. The Examiner states that:

> Given the teachings of Le et al. to treat rheumatoid arthritis as well as targeting

> TNF in various tissues including joints (see column 34, paragraphs 3-4), one of ordinary skill in the art at the time the invention was made would have been motivated to target various conditions associated with ankylosis as taught by the Merck Manual, since the ordinary artisan would have an expectation of success in inhibiting the deleterious inflammatory responses associated with limiting joint movement common to various conditions associated with ankylosis.

To establish a *prima facie* case of obviousness, where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)) "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* There must also be motivation or suggestion in the prior art to combine elements in the prior art. That is, in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. (*In re Newell* 13 USPQ2d 1248, 1250 (Fed. Cir. 1989))

As discussed above, Applicants' priority application, Le *et al.* U.S. Patent No. 5,698,195, is not prior art under 35 U.S.C. § 102 (b). It is also not prior art under 35 U.S.C. § 102 (a) or § 102 (e) because the publication is not "by another." The inventors listed in Le *et al.* U.S. Patent No. 5,698,195 are identical to the inventors of the subject application. In addition, the other cited reference, The Merck Manual of Diagnosis and Therapy, does not teach or suggest treatment of ankylosis with Applicants' recited cA2-specific anti-TNFα antibodies. Applicants claimed method of treating TNFα-mediated joint ankylosis with the recited cA2-specific anti-TNFα antibodies is not *prima facie* obvious, because one cited reference is not prior art and the other reference provides neither the requisite suggestion nor a reasonable expectation of success to arrive at the claimed invention.

Therefore, the rejection is moot. Reconsideration and withdrawal of the objection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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